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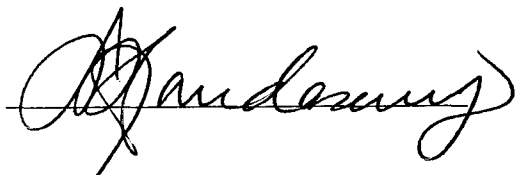
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13. ABSTRACT (Maximum 200 Words) BACKGROUND: No study has reported the risk factors and cancer screening practices associated with a diagnosis of breast carcinoma in-situ (BCIS), across all categories of age and histology. METHODS: The data are from a population-based case/control study which includes all female cases of BCIS diagnosed among residents of the state of Connecticut from 9/15/94 to 3/14/98 as well as a series of random-digit-dial (RDD) controls. Cases (n=1068) were between the ages of 20 and 79 years at time of diagnosis while controls (n=999) were frequency matched to the cases by five-year age intervals. RESULTS: Cases with ductal carcinoma in-situ (DCIS) were more likely than controls to be older at age of first full-term pregnancy and at menopause, to have had a previous breast biopsy as well as fewer full-term pregnancies. In addition, DCIS cases were more likely to report a family history of breast cancer particularly at a young age. With respect to cancer screening, DCIS cases were more likely than controls to have had at least one screening mammogram and to be receiving yearly breast exams by a physician. Cases with lobular carcinoma in-situ (LCIS) were more likely than controls to be older at menopause, to have had at least one breast biopsy and yearly physician-performed breast exams. No association was found between oral contraceptive use or hormone replacement therapy (HRT) and BCIS risk nor was there an association seen between diagnosis and use of breast self examination (BSE). Screening was significantly associated with a number of breast cancer risk factors including race, family history, HRT use and a previous breast biopsy. CONCLUSIONS: The risk factors for BCIS are similar to many of those associated with invasive breast cancer. The diagnosis of BCIS is associated with the use of mammography and yearly physician-performed breast examinations but not with BSE. In these data, utilization of these three screening methodologies varies significantly with race, a family history of breast cancer, HRT, and a previous breast biopsy.

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THE GENETIC EPIDEMIOLOGY OF BREAST CARCINOMA IN SITU

4.   INTRODUCTION

Breast cancer remains one of the most important health care issues of the 20th century. Despite a wealth of studies on the topic, the current literature provides little information regarding the nature of the epidemiologic risk factors or clinical characteristics of breast tumors which are classified as non-invasive, i.e., breast carcinoma in situ (BCIS). As screening efforts throughout the United States have increased, so has the number of women diagnosed with BCIS, with up to 20% of screened patients diagnosed with this lesion. The identification of risk factors associated with the development of BCIS is especially important, particularly in light of the fact that in the coming century up to one in fifty women in the United States will be diagnosed with this tumor during her lifetime. This project will define risk factors associated with BCIS through the mechanism of a case/control study. The study population includes 1068 cases of female breast carcinoma in situ and 999 age-matched female controls selected from the population of the state of Connecticut over a 3.5 year data collection period. Cases are between the age of 20 and 79 years at time of diagnosis. The controls are frequency matched to the cases by five year age intervals. Telephone interviews were conducted with the study subjects and collected information concerning family history of cancer, pregnancy and menstrual history, hormone replacement therapy, oral contraceptive use, fertility drug use, as well as sociodemographic variables. The expression of estrogen and progesterone receptors (ER and PR) as well as two of the most frequently reported oncogenes associated with invasive breast cancer, p53 and c-erbB-2, will be examined in these BCIS cases for the first time in a population-based series.

The goals of this study are as follows:

1. To determine whether there is an association between a family history of breast and/or ovarian cancer and the development of breast carcinoma in situ (BCIS).

2. To determine whether there is an association between additional epidemiologic risk factors, including those traditionally associated with invasive breast carcinoma such as age at menarche, age at first birth, and oral contraceptive use and the development of BCIS.

3. To collect paraffin-embedded tumor tissue for a subset of the BCIS cases.

4. To test for the presence of p53 and c-erbB-2 protein expression as well as estrogen and progesterone receptor expression using the methods of immunohistochemistry in the paraffin-

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embedded tumor tissue.

5. To examine the association between p53, ER, PR and/or c-erbB-2 expression in BCIS tumors with clinical and epidemiologic variables including grade and family history of breast cancer.

6. To develop risk prediction models to be used in defining screening guidelines for women not yet diagnosed with BCIS.

Specific Location of Study

Drs. Claus and Holford have offices located in the Department of Epidemiology and Public Health. Dr. Carter has an office and laboratory located within the Pathology Department. Dr. Badve, who now works with the project as a consultant, is located in the Department of Pathology at Northwestern University in Chicago. The offices of the project director and the director of the Rapid Case Ascertainment Shared Resource are located at 200 College Street, New Haven, CT.

5.   BODY

RESEARCH PLAN

The cases were ascertained through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center. The physicians of each eligible case were identified by the RCA. The names of patients and physicians were given to the project director by RCA staff. A letter signed by Dr. Claus and the project director was sent to the physicians requesting permission to send a letter of introduction to the case.

Proto-controls were identified by Northeast Research in Orono, Maine through the mechanism of random-digit dialing. Female residents of the state of Connecticut aged 20-79 who were served by a telephone were eligible.

Those cases approved for contact by their physicians were sent a letter of introduction from Dr. Claus and the project director explaining the project. Controls received a similar letter. Informed consent forms accompanied the letter of introduction and study subjects were asked to return them via the stamped, addressed envelope provided. Approximately 1-2 weeks later an interviewer (either Ms. Sheila Griffin or Ms. Marjorie Jasmin) contacted the potential study subject by telephone. If the potential study subject decided to participate, the interviewer administered the questionnaire over the telephone at the patient's convenience after verbal consent had been given for the interview. Subjects who agreed to be interviewed were sent an oral

contraceptive picture booklet with an accompanying letter. Subjects were interviewed for an average of 43 minutes. The questionnaire included questions on family history of cancer, pregnancy and menstrual history, oral contraceptive and other exogenous hormone history, medical history, socioeconomic status, as well as alcohol and tobacco use.

Pathology slides and histologic specimens were collected in the form of paraffin-embedded tumor tissue. Cases who agreed to allow us to retrieve paraffin-embedded blocks were sent an authorization of health information form that we then asked them to return via mail. RCA requests and couriers slides and paraffin-blocks from each of the pathology departments as well as returns the slides and blocks after the laboratory analyses are completed. The blocks are returned to the various hospitals after sufficient material has been removed from them. Alternatively, hospitals may choose to cut material from the blocks rather than send the block itself. The slides are quickly returned after our pathologists have reviewed them to confirm the diagnosis.

Medical records were reviewed to provide details requested in the questionnaire regarding dates of diagnoses or pathologic details of diagnosis. In particular, pathology data are useful in identifying tumor blocks most likely to contain tumor. A stamped, addressed envelope is provided for study subjects so that they may return the authorization for release of health information (for review of medical records and retrieval of paraffin-blocks) via mail. The project director telephoned study participants who did not return the form to encourage them to do so. Replacement forms were sent to women who misplace the original form.

YEARLY REPORT

The personnel on the project remained stable with the sole change being the identification of a new project director, Ms. Lisa McKay. Our previous project director, Mr. Thy Do, graduated and Ms. McKay has been hired to finish the work on this grant as well as continue as the project director on our new grant. This new grant, from the NIH, will fund a five-year followup study of the cases and controls in this data set and allow us to continue to collect paraffin blocks for immunohistochemical studies.

Over the study period, 1606 proto-cases and 1445 proto-controls were identified. One hundred and eleven cases were ineligible due to out-of-state residency (8), language (21), a history of previous breast cancer/biopsy of unknown outcome (51), and age-group (31). Ninety-one percent of eligible cases had a consenting physician. Among eligible cases who were contacted by our study, 83% participated in the interview portion of the study. Two hundred and four controls were ineligible due to out-of-state residency (3), language (18), a history of previous breast cancer/biopsy of unknown outcome (181), and age-group (2). Among eligible controls who were contacted by our study, 81% agreed to be interviewed. The final sample included 1068 case and 999 control subjects.

In addition to the interview portion of the study, we completed the histologic slide/pathology review portion of the study. Slides were obtained and reviewed for approximately 83% of interviewed cases. Among cases, 83.6% were diagnosed with DCIS, 11.7% with LCIS, and 4.7% with mixed or other pathology.

We are continuing to retrieve blocks for those women who have given permission. This portion of the study has proved to be very time-consuming as many of the hospitals in the state have put a hold on the release of biologic specimens. In fact, just last month, Hartford Hospital finally agreed to release blocks to us after two years of negotiations by RCA. At present we have received and/or stained approximately 350 blocks and will continue to collect and stain them during our five-year followup.

Data analysis continued this year with two manuscripts under review (copies are enclosed): "Breast carcinoma in-situ: Risk factors and screening patterns" and "Family history of breast and ovarian cancer and the risk of breast carcinoma-in situ". Results from the first manuscript were presented at the DOD meeting in Atlanta in June 2000. Two additional manuscripts are near completion: "Oral contraceptive use and the risk of breast carcinoma in-situ" and "Segregation analysis of breast carcinoma in-situ". In addition, we are happy to report that the work done on this Army grant has helped us to receive an NIH grant to continue our work and follow the study subjects for five years.

HUMAN SUBJECTS

Subject Population

All female Connecticut residents between the ages of 20 and 79 years at time of diagnosis and diagnosed with breast carcinoma in situ from 9/15/94 to 3/14/98 were eligible. Cases with a previous history of breast cancer and/or a breast biopsy of unknown outcome were excluded. In this time period, 1606 women were diagnosed with BCIS in the state of Connecticut within the age-group of interest. From this group, we interviewed 1068 women. Proto-controls were randomly selected by an external firm (Northeast Research) and consist of age-matched Connecticut female residents. We identified 1445 proto-controls and interviewed 1048 as controls. (Of note, upon interview, 49 controls reported a history of breast cancer and were not included in the final count as study controls. The final count is therefore 999 controls.)

Risks/Benefits

As this is primarily an interview study, we anticipate no physical risk to study subjects. However, given the serious nature of breast cancer, it is conceivable that some patients will experience some degree of psychological distress as a result of being interviewed concerning their health status. In order to minimize the occurrence of such distress, interviewers are trained to conduct interviews in a relaxed, friendly, and professional manner. Swift corrective action will be taken concerning any interviewer whose demeanor seems to have a negative effect on study participants.

There are no monetary inducements to participants in this study. The primary inducement for participants is the ability of the study to contribute to our understanding of breast cancer. This research has the potential to define modifiable risk factors associated with the development of breast cancer as well as the potential to identify currently healthy women at increased risk of this disease who might benefit from increased screening for breast cancer.

At present no adverse effects have been reported in this study. A number of positive effects have been reported, particularly to our interviewers, including the improvement of family relationships in association with the gathering of family history information. In addition, among cases, the discussion of a breast cancer diagnosis with an independent observer has proved to be helpful to a number of women.

Protection of Subjects

Each study subject is assigned a code number. The interview cover sheet containing identifying information is removed from the interview booklet and stored separately. All staff members are informed prior to employment and at regular intervals as to the necessity for keeping all data confidential. All written study material is stored in locked file cabinets. All histologic specimens will be stored in the laboratory of Dr. Carter.

The opinion of Dr. Carter, the study pathologist, concerning histologic specimens may in some instances differ from that of the original pathologist. If Dr. Carter interprets the woman's cancer to be invasive rather than solely in-situ, the original pathologist and surgeon will be contacted and informed of the opinion of the study pathologist. If the original pathologist is not available, we will inform the Chair of Pathology at the appropriate hospital.

No information that identifies an individual subject will be given to third parties, including family members, unless that subject has given consent to do so. Information obtained during the study will not be placed in a subject's medical record. Publication and presentation of results will contain only aggregate data.

No laboratory test results on specimens will be released to the participant or her physician. This current work is in the realm of research and any results should be regarded as preliminary findings and not definitive. None of the materials collected on these patients will be used to do research unrelated to their breast cancer diagnosis.

Human Investigation Committee Approvals

We have had great success in obtaining the approval and participation of the state's hospitals. At present, all but four of the state's 32 hospitals are active participants. We are able to identify cases diagnosed and treated at these four hospitals via the Connecticut Tumor Registry. Overall, the response of the state's hospitals and medical personnel has been extremely positive. Most of the hospitals are now in their sixth year of participation with our study.

6. KEY RESEARCH ACCOMPLISHMENTS/REPORTABLE OUTCOMES/CONCLUSIONS

The study represents the first large population-based case/control study of breast carcinoma in-situ with data collected across all age-categories and histologic subtypes, and with information on screening variables such as mammography. Data from the project were presented at the DOD meetings in both 1998 and 2000. There are two manuscripts under review at present (see Appendices A and B) and two in preparation (listed above). We have applied for and received funding from the National Institutes of Health to continue our work on these study subjects in the form of a five-year R01 grant. The goal of the new grant is to provide five-year follow-up for these women to describe the outcomes of women with BCIS and to define possible risk factors associated with morbidity and mortality in these women. We are also applying for additional funding to study mammographic risk factors and the development of BCIS.

BREAST CARCINOMA IN-SITU:

RISK FACTORS AND SCREENING PATTERNS

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ABSTRACT

BACKGROUND

Although numerous studies have defined risk factors for invasive breast carcinoma, no study has reported the risk factors and cancer screening practices associated with a diagnosis of breast carcinoma in-situ, across all categories of age and histology.

METHODS

The data are from a large, population-based case/control study which includes all female cases of breast carcinoma in-situ (BCIS) diagnosed among residents of the state of Connecticut from September 15, 1994 to March 14, 1998 as well as a series of random-digit-dial (RDD) controls selected from the state of Connecticut. Cases (n=1068) were between the ages of 20 and 79 years at time of diagnosis while controls (n=999) were frequency matched to the cases by five-year age intervals. Telephone interviews were used to collect information on family history of cancer, pregnancy and menstrual history, exogenous hormone use, as well as socio-demographic variables and cancer screening history.

RESULTS

Cases with ductal carcinoma in-situ (DCIS) were more likely than controls to be older at age of first full-term pregnancy and at menopause, to have had a previous breast biopsy (odds ratio (OR): 3.34, 95 percent confidence interval (95CI): 2.70 to 4.15) as well as fewer full-term pregnancies. In addition, DCIS cases were more likely to report a family history of breast cancer particularly at a young age; results for women aged 49 years or younger (OR: 2.36;95CI, 1.47 to 3.77) versus for women older than 49 years (OR: 1.36, 95CI: 1.01 to 1.85). With respect to cancer screening, DCIS cases were more likely than controls to have had at least one screening mammogram (OR: 2.46,

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95CI: 1.78 to 3.40) and to be receiving yearly breast exams by a physician (OR: 1.83, 95CI: 1.48 to 2.26). Cases with lobular carcinoma in-situ (LCIS) were more likely than controls to be older at menopause, to have had at least one breast biopsy (OR: 4.12, 95CI: 2.33 to 7.29) and yearly physician-performed breast exams (OR: 2.37, 95CI: 1.44 to 3.90). An association between family history of breast cancer and a diagnosis of LCIS was suggested but did not reach statistical significance (OR: 1.69, 95CI: 0.97, 2.96). No association was found between oral contraceptive use or hormone replacement therapy (HRT) and BCIS risk nor was there an association seen between diagnosis and use of breast self examination (BSE). Screening was significantly associated with a number of breast cancer risk factors including race, family history, HRT use and a previous breast biopsy.

CONCLUSIONS

The risk factors for BCIS are similar to many of those associated with invasive breast cancer. The diagnosis of BCIS is associated with the use of mammography and yearly physician-performed breast examinations but not with BSE. In these data, utilization of these three screening methodologies varies significantly with race, a family history of breast cancer, HRT, and a previous breast biopsy.

Word Count: 2781

Keywords: Breast carcinoma in situ, risk factors, epidemiology, ductal carcinoma in situ, lobular carcinoma in situ

INTRODUCTION

As mammographic screening efforts have increased, so has the number of breast tumors which are classified as non-invasive, i.e. breast carcinoma in situ (BCIS), with up to 20% of screened breast cancer patients diagnosed with

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this lesion. Few studies have examined the epidemiology of BCIS.[2-15] Previous

attempts to define risk factors have focused on small subsets of BCIS cases

nested within larger invasive breast cancer (IBC) case/control[3,4,13] studies or

screened cohorts.[6,9,14] A recent population-based study of 1616 breast cancer

cases aged under 45 years and which included 228 BCIS cases, reported that

both ductal (DCIS) and lobular (LCIS) in situ cancer were positively

associated with many established IBC risk factors including a family history

of breast cancer, previous breast biopsy, and nulliparity.[3] A second

population-based case/control study which included 233 in-situ cases aged 40

and younger or between 55-64 years, also reported an increased risk of BCIS

with family history and benign breast disease.[4] However, in premenopausal

women, the risk of in-situ lesions relative to invasive disease decreased with

increasing body mass index while in postmenopausal women, use of unopposed

estrogen replacement was associated with increased risk of in-situ cancer

relative to women with invasive disease. Data from additional case-control

analyses obtained from cohorts of screened women report increased risk

associated with age[9,14], a positive family history of breast cancer[6,9], race[14],

nulliparity[9], a previous breast biopsy[6], and increased age at first

livebirth[6,9]

The above mentioned studies provide evidence that many risk factors

associated with IBC may also play a role in the development of BCIS. The

results, however, are not consistent across studies. In many instances, small

sample size does not allow for precise estimates of risk. In general,

information on screening variables is not available;[4,6,8,9] in the one study

that did collect such information, no data are available for cases over 45

years of age.[3] Furthermore, only one study has presented separate analyses by

histologic subtype and again, only for women under the age of 45 years.[3] The

data presented here represent the first large, population-based study

specifically designed to examine the association between risk factor history

and BCIS diagnosis across the full spectrum of age and histology, while

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incorporating data on cancer screening.

METHODS

The study population includes all cases of female BCIS diagnosed among residents of the state of Connecticut from September 15, 1994 to March 14, 1998 as well as a series of age-matched controls. Cases were identified through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center and were between the ages of 20 and 79 years at time of diagnosis. Controls were female Connecticut residents selected by random-digit dialing methods and were frequency matched by five-year age intervals to the cases. Study subjects with a previous history of breast cancer and/or a breast biopsy of unknown outcome were excluded. The study, consent forms and questionnaire were approved by the Yale University School of Medicine Human Investigation Committee.

The physicians of each eligible case were contacted to request permission to approach the case. Cases approved for contact by their physicians and controls were sent a letter of introduction. Approximately 1-2 weeks later a trained interviewer contacted the potential study subject by telephone. If a woman decided to participate, the interviewer administered the questionnaire over the telephone at the subject's convenience. Women who consented to be interviewed were sent an oral contraceptive picture booklet developed for the Harvard University Nurses' Health Study[16] to allow them to review products used in the past. Subjects were interviewed for an average of 43 minutes. The questionnaire included detailed questions on family history of cancer, pregnancy and menstrual history, exogenous hormone history, demographics, medical and screening history, and smoking and alcohol consumption.

Over the study period, 1606 proto-cases and 1445 proto-controls were identified. Eighty cases were ineligible due to out-of-state residency (8),

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language (21), or a history of previous breast cancer/biopsy of unknown outcome (51), and age-group (31). Ninety-one percent of eligible cases had a consenting physician. Among eligible cases who were contacted by our study, 83% participated in the interview portion of the study. Two hundred and four controls were ineligible due to out-of-state residency (3), language (18), a history of previous breast cancer/biopsy of unknown outcome (181), and age-group (2). Among eligible controls who were contacted by our study, 81% agreed to be interviewed. The final sample included 1068 case and 999 control subjects.

Cases were defined as in-situ, either ductal (DCIS) or lobular (LCIS), if they were non-infiltrating. All cases were confirmed by pathology report. Cases with mixed or other pathology were not included in any analyses. Risk factor information was truncated at the date of diagnosis for cases and the date of interview for controls. Data on screening variables consisted of five questions which asked for the commencing age, frequency, and date of most recent routine checkup, breast exam by a physician, breast self-exam (BSE), pap smear, and mammogram one year prior to the diagnosis/interview.

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. T-tests and chi-square tests were used to examine the association between the risk of BCIS and independent covariates. To assess the relative risk of BCIS associated with risk factors, logistic regression was used to provide maximum likelihood estimates of the odds ratios (ORs) (adjusted and unadjusted) with 95% confidence intervals (CIs) using the statistical package PC-SAS version 6.11.[17]

RESULTS

Approximately 92 percent of the cases and controls were white with the

remaining eight percent representing primarily women of African-American background (6.5%). Thirty-four percent of cases were college-educated versus 28% of controls. Cases were older on average than controls (57.4 versus 55.9 years). Because of the statistically significant differences in education and age, all risk estimates were adjusted for both of these variables. Among cases, 83.6% were diagnosed with DCIS, 11.7% with LCIS, and 4.7% with mixed or other pathology. Among women diagnosed with DCIS, 66% had their lesion discovered by mammogram versus 8% by self-exam, 11% by accident, and 10% by a physician. LCIS cases reported discovery rates of 17%, 16%, 34%, and 20%, respectively.

The proportions of women who participated in various cancer screening procedures is presented by case/control status in Table 1. DCIS cases were more likely than controls to have received at least one screening mammogram one year prior to interview (OR: 2.46, 95CI: 1.78, 3.40) as well as yearly physician breast exams (OR: 1.83, 95CI: 1.48, 2.26) but were as likely as controls to be performing BSE (OR: 1.01, 95CI: 0.84, 1.21). When examining the percentages of women under 45 years, 78% of DCIS cases and 62% of controls reported ever having had a mammogram. Cases with LCIS were more likely to report having a yearly physician performed breast exam (OR: 2.37, 95CI: 1.44, 3.90) but no more likely to report use of mammography (OR: 1.81, 95CI: 0.92, 3.55) or BSE (OR: 0.89, 95CI: 0.61, 1.31).

The age-adjusted proportion of study subjects participating in mammography, yearly physical exam, and monthly BSE one year prior to interview is presented by breast cancer risk factor profile in Table 2. Women with a first degree family history of breast cancer were more likely to have had a mammogram (OR= 2.4, 95% CI: 1.5, 3.9), a yearly breast exam by a physician (OR = 1.5, 95% CI: 1.2, 1.8), and have practiced monthly BSE (OR = 1.2, 95% CI: 1.1, 1.5) than were women who did not report such a history. Among women with a family history, those with an affected mother (OR 3.20, 95CI: 1.55, 6.60) were almost twice as likely to have undergone at least one mammogram relative

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to those with an affected sister (OR 1.47, 95CI: 0.76, 2.86). HRT users were

four times as likely to undergo mammography and over twice as likely to be

undergoing yearly physician breast exams relative to women who did not receive

HRT. White women were more likely than non-white women to have received a

mammogram, equally likely to report a yearly physician breast exam and less

likely to report doing BSE. Study subjects who reported having had at least

one breast biopsy also reported a higher rate of all three screening

modalities relative to women without such a history, while college-educated

women were more likely to have had a yearly physician breast exam (p = 0.05)

but equally likely to have had a mammogram or practiced BSE relative to women

without such an education.

Multivariate adjusted odds ratios of BCIS are presented, by histologic

subtype, in Table 3. Among women diagnosed with DCIS, cases were significantly

more likely than controls to be older at age of first full-term pregnancy and

at menopause (borderline significance). In addition, DCIS cases were more

likely to report a first degree family history of breast cancer, to be

nulliparous, to have fewer full-term pregnancies, and to have had at least one

breast biopsy. An inverse association was seen between age at onset and family

history with respect to risk; cases diagnosed prior to age 50 were 2.34 (95CI:

1.47, 3.77) times more likely than controls to report having an affected first

degree relative versus an odds ratio of 1.36 (95CI: 1.01, 1.85) for cases

diagnosed at 50 years or older. No significant differences were appreciated

between DCIS cases and controls with respect to race, age at first menstrual

period, oral contraceptive (OC) or HRT or by history of smoking or alcohol

use. Because of the association between case/control status and mammography

utilization, all odds ratios are adjusted for mammogram history. Additional

adjustment for other breast cancer screening methods did not significantly

alter the odds ratios (primarily due to correlation between the screening

variables) and hence were not included in the final model. The analyses were

also performed retaining the original frequency-matched study design (five-

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year age strata); the results obtained were essentially unchanged from those presented in Table 3.

Women diagnosed with LCIS were more likely than controls to be older at menopause, to have had at least one breast biopsy and to be undergoing yearly physician-performed breast exams. An association between family history of breast cancer and a diagnosis of LCIS was suggested but did not reach statistical significance (p = 0.07). The data were too sparse to examine the role of age at onset in this relationship. As can be seen from Table 3, the magnitude and direction of many risk factors were the same for the two histologic subtypes, although in several instances the risk factor reached statistical significance for DCIS but not LCIS cases, likely due in part to the much smaller number of LCIS cases relative to DCIS cases.

DISCUSSION

The epidemiology of IBC has been extensively studied.[18-26] Among those variables that have been shown to bear a relationship with IBC, the greatest increase in risk (2-3 fold), after controlling for age, has generally been associated with the presence of a positive family history.[18-26] Individuals with multiple first degree family members diagnosed with ovarian or breast cancer, particularly at young ages, are at even greater risk. Examination of such families has led to the identification of several breast/ovarian cancer susceptibility alleles (BRCA1, BRCA2).[27,28] Little work has specifically examined the effect of a family history on the risk of BCIS with existing data hampered by limitations of sample size, age at onset or pathology. Despite these caveats, the existing studies uniformly report an increased risk associated with family history with odds ratios ranging from 1.6 to 2.7 [3,4,6,9,10] similar to those observed for IBC. The current study confirms this finding in a large sample, with odds ratios of 1.6 and 1.7 for women diagnosed with DCIS and LCIS, respectively. These values generally match well to studies which include women of similar age range[6] but are somewhat lower than studies

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which include relatively younger women.[3,4,9] However, when risk is dichotomized

by age in these data, an inverse relationship is seen between age at onset and

risk associated with family history with cases diagnosed by age 49 reporting a

risk of 2.4, similar to other reports which include young cases[3,4,9] versus a

risk of 1.4 for cases diagnosed over the age of 49 years. This association

between age at onset, family history and breast cancer risk is well documented

for IBC; it is likely that this relationship also exists for BCIS and may

suggest a role for breast cancer susceptibility alleles such as BRCA1 and

BRCA2, although there is currently little data to suggest that mutations in

these alleles occur with any frequency in women with BCIS.[29] A positive

association between family history and LCIS risk was also suggested here as

has been reported elsewhere.[3,13] As with previous reports, it is likely that

limitations of sample size may have reduced the power to obtain a significant

result in these data.

Additional variables associated with IBC risk include those with

endogenous or exogenous hormonal components such as nulliparity, age at first

livebirth, age at menarche and menopause, as well as (in some subgroups) OC

and HRT use. In general, these risk factors have been associated with 1.5-2

fold increases in breast cancer risk. In these data risk was associated with

several of the same factors. In particular, DCIS cases were more likely than

controls to be older at first full-term pregnancy and at last menstrual period

and to have fewer full-term pregnancies. The data also suggest a reduction in

risk with a later age at first menstrual period, however this effect did not

reach statistical significance. The results from this analysis as well as

previous examination of such variables appear to confirm an association

between in-situ risk and later age at first full term pregnancy[4,6,9,10,11],

nulliparity[3,9,10,11], and later age at menopause[4]. No association was seen in

these data between either OC or HRT use and in-situ risk. To our knowledge,

this is the first estimate of the relative risk associated with OC use and

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BCIS. The role of HRT in BCIS has been previously explored although the results are not uniform and the sample sizes are small; several[4,30,31]but not all[32] of the few previous studies report an increase in risk.[4,30,31] Although it is possible that some of this effect may be the result of increased screening among HRT users versus non-users, the studies mentioned all made some attempt to adjust for screening history. To further explore the relationship between exogenous hormones and the development of BCIS, detailed analyses will be presented elsewhere to define the role of age, duration, frequency, composition, and potency on this relationship.

As has been reported in a number of studies[3,4,6,9,10], a history of breast biopsy is strongly correlated with a diagnosis of both DCIS and LCIS in these data. The association between benign breast disease and IBC is well known. The correlation reported here between BCIS diagnosis and biopsy is likely due to a combination of factors, including the likelihood that some benign breast disease is associated with the eventual development of BCIS. This observed correlation is also likely a function of increased surveillance and hence early detection; it is not possible at present to quantify the extent to which each of these possibilities plays a role in this significant association.

There were a number of significant associations between screening patterns and risk factors. At least within the state of Connecticut, women with either a family history of breast cancer or a previous breast biopsy appear to be receiving more intensive screening than those without such a history. Race was also significantly associated with screening frequency; in these data, white women were twice as likely as non-white women to report having had a screening mammogram but 30% less likely to practice BSE. This is of note given the increased rates of BCIS diagnosis associated with mammography use but not with BSE. The risk factor most strongly associated with screening in these data was use of HRT. The magnitude of this association is large (fourfold); it is notable that women with this risk factor were almost twice as likely as women with a first degree family history to receive

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a mammogram.

This study provides evidence that many of the risk factors for BCIS are similar in nature and magnitude to those for IBC, lending support to the hypothesis that some in-situ lesions may be a part of the causal pathway leading to invasive disease. These data represent the largest examination to date of the epidemiology of BCIS across all categories of age and histology. Furthermore, as information on screening was included in all analyses, the estimates of risk presented here should be relatively free of screening bias, particularly important in the analysis of non-invasive tumors which are more likely to be diagnosed at an early stage using screening procedures such as mammograms.

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Table 1. Percentage of women undergoing screening[a] stratified by case/control status.			
	Study Subject		
Screening Modality	DCIS	LCIS	Controls
Mammogram (Ever/Never)	93.3%[b]	91.2%	85.4%
No. Mammograms			
None	6.3%	8.1%	14.8%
One	5.0%	8.1%	0.8%
Two or more	88.7%	74.8%	84.4%
Breast Self Examination	43.5%	40.6%	43.3%
Physician Breast Exam	79.9%[b]	83.7%[b]	68.5%
Pap Smear	97.6%	96.8%	97.3%

a. One year prior to diagnosis for cases/interview for controls.
b. Significantly different from controls at p = 0.05.
c. Significantly different from LCIS cases at p = 0.05.

Table 2. Percentage of women undergoing screening[a] stratified by breast cancer risk factors.

Risk Factor	Screening Method		
	Mammogram	Physician Exam	Breast Self Examination
First Degree Family History			
Yes	94.8%	79.2%	46.2%
No	88.5%	74.8%	42.8%
OR (95% CI)	2.4 (1.5, 3.9)[b]	1.3 (0.9, 1.7)	1.1 (0.9, 1.4)
Race (White)			
Yes	90.3%	75.7%	42.7%
No	82.2%	74.6%	50.3%
OR (95% CI)	2.0 (1.3, 3.1)[b]	1.1 (0.7, 1.5)	0.7 (0.5, 1.0)
Previous Breast Biopsy			
Yes	95.3%	80.5%	46.4%
No	86.1%	72.4%	41.4%
OR (95% CI)	3.2 (2.2, 4.6)[b]	1.6 (1.3, 1.9)	1.2 (1.0, 1.5)
Hormone Replacement [c] Therapy			
Yes	95.3%	82.3%	44.8%
No	83.3%	67.1%	42.2%
OR (95% CI)	4.0 (2.8, 5.8)[b]	2.3 (1.8, 2.8)	1.1 (0.9, 1.3)
College Education			
Yes	89.4%	77.9%	43.6%
No	89.8%	74.1%	43.2%
OR (95% CI)	1.0 (0.7, 1.3)[b]	1.2 (1.0, 1.5)	1.0 (0.8, 1.2)

a. One year prior to diagnosis for cases/interview for controls.
b. Adjusted for age (continuous).
c. Ever/Never

Table 3. Multivariate-adjusted Odds Ratios (OR) for breast cancer according to the level of risk factors, stratified by case histology.[a]

	Number of			OR (95% CI)		
	DCIS	LCIS	Controls	DCIS	LCIS	LCIS vs DCIS[b]
Age at menarche (yr)						
#11	173	31	187	1	1	1
12	232	32	240	1.03 (0.76,1.39)	1.47 (0.67, 3.21)	1.74 (0.80, 3.79)
13	253	29	292	0.88 (0.66,1.17)	0.66 (0.28, 1.60)	0.80 (0.34, 1.91)
∃14	203	29	260	0.80 (0.59,1.09)	1.01 (0.44, 2.30)	1.42 (0.62, 3.26)
x^2 for trend				0.96 (0.90,1.02)	0.96 (0.82, 1.14)	1.03 (0.87, 1.23)
Previous breast biopsy						
No	420	31	788	1	1	1
Yes	455	92	211	3.34 (2.70,4.15)	4.12 (2.33, 7.29)	1.20 (0.69, 1.71)
Family history						
No	553	73	721	1	1	
Yes	322	50	278	1.56 (1.19,2.03)	1.69 (0.97, 2.96)	1.14 (0.66, 1.99)
Number full-term pregnancies						
No	166	23	127	1	1	1
Yes (per FTP)	709	100	872	0.86 (0.80,0.93)	0.99 (0.80, 1.23)	1.14 (0.94, 1.39)
Age at first live birth (yr)[c]						
<20	86	8	144	1	1	1
20-29	515	82	604	1.60 (1.12,2.30)	1.53 (0.54, 4.32)	0.96 (0.33, 2.81)
30+	108	10	124	1.79 (1.14,2.81)	0.74 (0.17, 3.17)	0.46 (0.10, 2.01)
x^2 for trend				1.03 (1.00,1.05)	0.99 (0.92, 1.06)	0.97 (0.90, 1.04)
Age at menopause (yr)[d]						
<45	186	23	209	1	1	1
45-49	184	19	164	1.31 (0.95,1.82)	1.09 (0.39, 3.05)	0.60 (0.21, 1.67)
50-54	196	26	191	1.09 (0.79,1.51)	2.05 (0.85, 4.96)	1.59 (0.67, 3.79)
55+	63	6	50	1.55 (0.97,2.48)	2.35 (0.65, 8.54)	1.39 (0.40, 4.81)
per yr				1.01 (0.99,1.03)	1.06 (1.01, 1.12)	1.04 (0.98, 1.09)
Ever use of OC						
No	471	62	477	1	1	1
Yes	404	61	522	0.94 (0.74,1.21)	0.55 (0.29, 1.04)	0.55 (0.39, 1.02)
Ever use of HRT						
No	431	55	563	1	1	
Yes	430	65	423	1.17 (0.94,1.44)	1.34 (0.74, 2.40)	1.29 (0.72, 2.30)

Ever smoke						
No	388	58	434	1	1	1
Yes	485	65	562	1.02 (0.82,1.25)	1.03 (0.58, 1.81)	0.94 (0.54, 1.65)
Ever Drink						
No	335	37	346	1	1	1
Yes	537	85	650	0.93 (0.74, 1.16)	1.07 (0.58, 1.98)	1.22 (0.66, 2.23)

a. Adjusted for age (continuous), college education (yes/no), history of at least one screening mammogram one year prior to interview, quetelet index, race (white/other) and mutually adjusted for the other variables in the table.
b. Odds of LCIS relative to DCIS for a given risk factor
c. Results for age at first birth are for parous women only
d. Results for age at menopause are for post-menopausal women only and include both surgical and natural menopause

Appendix β

FAMILY HISTORY OF BREAST AND OVARIAN CANCER

AND THE RISK OF BREAST CARCINOMA IN-SITU

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ABSTRACT

CONTEXT

A family history of breast cancer is an important risk factor for in-situ breast carcinoma (BCIS), however there are no detailed analyses of its variation in effect by number, type, laterality or age at onset of affected relatives nor by association with ovarian cancer. In addition, the role of the breast cancer susceptibility genes, BRCA1 and BRCA2, in the development of BCIS is unclear.

OBJECTIVE

To better define the role of 1) a family history of breast and ovarian cancer and 2) the cancer susceptibility genes, BRCA1 and BRCA2, in the development of BCIS.

DESIGN, SETTING, AND PARTICIPANTS

The data are from a large, population-based case/control study of BCIS and includes all female cases of BCIS diagnosed among residents of the state of Connecticut from September 15, 1994 to March 14, 1998 as well as a series of random-digit-dial (RDD) controls selected from the state of Connecticut. Cases (n=1068) were between the age of 20 and 79 years at time of diagnosis while controls (n=999) were frequency matched to the cases by five-year age intervals. Telephone interviews were used to collect information on family history of cancer, pregnancy and menstrual history, hormone replacement therapy, oral contraceptive use, as well as socio-demographic variables and cancer screening history.

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MAIN OUTCOME MEASURE

To assess the relative risk of BCIS associated with breast and ovarian cancer family history, logistic regression was used to provide maximum likelihood estimates of the odds ratios (OR) with 95% confidence intervals (95CI). The probability of being a BRCA1 and/or BRCA2 gene carrier is calculated for each case and control, using family history of breast and ovarian cancer, age/age at diagnosis for relatives, prevalence and penetrance data for BRCA1/BRCA2, and self-report of Jewish heritage.

RESULTS

Cases with ductal carcinoma in-situ (DCIS) or lobular carcinoma in-situ (LCIS) were significantly more likely to report a first degree family history of breast cancer (OR: 1.7, 95CI: 1.3, 2.1 for DCIS versus OR: 1.8, 95CI: 1.2, 2.9 for LCIS cases) than were controls. In addition, DCIS cases were 2.6 (95CI: 0.9, 7.3) times more likely than controls to report both an affected mother and sister. An inverse association was suggested between age at onset and DCIS risk with cases aged 49 years or younger at 2.4 (95CI: 1.5, 3.8) times the risk of controls (95CI) versus 1.5 (95CI: 1.1, 2.0) for cases older than 49 years. Cases and controls did not differ significantly with respect to the proportion of family members affected with ovarian cancer (OR: 1.2, 95CI: 0.8, 1.8).

The predicted probability that a woman represents a carrier of either BRCA1 or BRCA2 differed significantly by case/control status as well as (for BRCA1) by age at onset. In these data, approximately 0.1% of DCIS cases were predicted to carry a mutation in BRCA1.

CONCLUSIONS

A family history of breast cancer is associated with an increased risk of BCIS. Furthermore, as is true for invasive breast cancer, women with multiple family members affected with breast cancer, particularly at a young age, are at increased risk of BCIS. These data suggest the possibility that breast cancer susceptibility alleles such as BRCA1 and BRCA2 may also play a role in the development of BCIS, however, the results indicate that mutations in such alleles may occur less frequently in BCIS than is currently reported for invasive breast cancer.

INTRODUCTION

The association between a family history of breast cancer and invasive breast cancer (IBD) is well established[1-9] and there is compelling evidence to suggest that a similar association exists for breast carcinoma in-situ (BCIS)[10-17] In general, a family history of breast cancer has been associated with a two- to three-fold increase in the risk of IBD.[1-9] Results from BCIS studies report a similarly increased risk with odds ratios ranging from 1.5 to 2.7.[10-17] In more detailed analyses of family history in studies of IBD, researchers have found that individuals with multiple first degree family members diagnosed with ovarian cancer or breast cancer, particularly at young ages, are at even greater risk. Examination of such families with multiple members affected with early onset breast cancer as well as with ovarian cancer has led to the identification of several breast cancer susceptibility alleles (BRCA1, BRCA2).[18,19] The results from studies of invasive disease coupled with the observed increased risk of BCIS associated with a family history of breast cancer suggest that further analyses of BCIS risk by type, number, age at onset, and disease laterality of affected relatives are necessary to determine whether a similar genetic mechanism may play a role in BCIS risk. To our knowledge no existing study includes information on breast cancer history on any relative other than a mother and/or sister(s). In addition, no published data exist which incorporate information on the age at onset or laterality of any relatives affected with breast cancer nor any information on ovarian cancer among any relatives in the calculation of BCIS risk. The data presented here therefore represent the first large, population-based effort to examine in detail the association between a family history of either breast or ovarian cancer and a diagnosis of BCIS across the full spectrum of age and histologic

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subtype, while incorporating data on cancer screening history.

METHODS

The study population includes all cases of female BCIS diagnosed among residents of the state of Connecticut from September 15, 1994 to March 14, 1998 as well as a series of age-matched controls. Cases were identified through the Rapid Case Ascertainment (RCA) Shared Resource of the Yale Cancer Center and were between the ages of 20 and 79 years at time of diagnosis. Coverage of cancer cases by this service is considered essentially complete within the state of Connecticut. Controls were female Connecticut residents selected by random-digit dialing methods and were frequency matched by five-year age intervals to the cases. Study subjects with a previous history of breast cancer and/or a breast biopsy of unknown outcome were excluded. The study, consent forms and questionnaire were approved by the Yale University School of Medicine Human Investigation Committee.

The physicians of each eligible case were contacted to request permission to approach the case. Those cases approved for contact by their physicians were sent a letter of introduction explaining the project. Controls received a similar letter. Approximately 1-2 weeks later a trained interviewer telephoned the potential study subject. If a woman decided to participate, the interviewer administered the questionnaire over the telephone at the patient's convenience after verbal consent was given for the interview. Prior to the telephone interview, study subjects who had consented to be interviewed were sent an oral contraceptive picture booklet developed for the Harvard University Nurses' Health Study[20] to allow them to review products used in the past. Subjects were interviewed for an average of 43 minutes. The

questionnaire included detailed questions on family history of cancer, pregnancy and menstrual history, contraceptive and exogenous hormone history, demographic information, medical and screening history, and smoking and alcohol consumption.

Over the study period, 1606 proto-cases and 1445 proto-controls were identified. One hundred and eleven cases were ineligible due to out-of-state residency (8), language (21), a history of previous breast cancer/biopsy of unknown outcome (51), and age-group (31). Ninety-one percent of eligible cases had a consenting physician. Among eligible cases who were contacted by our study, 83% participated in the interview portion of the study. Two hundred and four controls were ineligible due to out-of-state residency (3), language (18), a history of previous breast cancer/biopsy of unknown outcome (181), and age-group (2). Among eligible controls who were contacted by our study, 81% agreed to be interviewed. The final sample included 1068 case and 999 control subjects.

Cases were defined as in-situ, either ductal (DCIS) or lobular (LCIS), if they were non-infiltrating. All cases were confirmed by pathology report. Cases with mixed or other pathology were not included in any analyses. Risk factor information was truncated at the date of diagnosis for cases and the date of interview for controls. Data on screening variables consisted of five questions which asked for the commencing age, frequency, and date of most recent routine checkup, breast exam by a physician, breast self-exam (BSE), pap smear, and mammogram one year prior to the diagnosis/interview. With respect to family history, study subjects were asked to provide the type, age at onset, and laterality (as appropriate) of up to three cancers for all male and female first degree (mother, father, sisters, brothers, daughters, and

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sons) and second degree relatives (maternal and paternal grandmothers and grandfathers, as well as aunts and uncles).

Statistical Analysis

The initial portion of the statistical analysis included descriptive statistics. T-tests and chi-square tests were used to examine the association between the risk of BCIS and independent covariates. To assess the relative risk of BCIS associated with risk factors, logistic regression was used to provide maximum likelihood estimates of the odds ratios (ORs) (adjusted and unadjusted) with 95% confidence intervals (CIs) using the statistical package PC-SAS version 6.12.[21]

The probability of carrying a mutation in BRCA1 or BRCA2 or both is calculated for each case and control (i.e. proband) using BRCAPRO.[22] The program employs a model which uses Bayes theorem and Mendelian genetics and assumes an autosomal dominant transmission for both BRCA1 and BRCA2.[23,24] In each instance, a woman's probability of being a gene carrier is calculated conditional upon the breast and ovarian cancer status of her first and second degree female relatives and the age at onset of any affected female relatives as well as the current age/age at death of any unaffected female relatives. The calculation of carrier probability also takes into account whether or not the proband was herself affected and whether she identified herself as Jewish in the questionnaire. The model uses BRCA1/BRCA2 prevalence estimates from Ford et al. (1995)[25] as well as penetrance estimates from Easton et al.(1995)[26] for women who did not identify themselves as Jewish and from Struewing et al.(1997) for women who did identify themselves as Jewish.[27] Differences in the mean carrier probability were examined by case/control status and 10-year

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age categories using analysis of variance.

To estimate the proportion of cases and controls who would be predicted to carry mutations in BRCA1, BRCA2 or either, study subjects were divided into two groups (carrier or non-carrier) by carrier probability, using 0.5 as the cutpoint. This cutpoint was selected based on sensitivity and specificity data collected on a sample of 125 patients with both BRCAPRO estimates and laboratory testing for BRCA1 and BRCA2[28] and on the fact that, in some instances, depending on available family history, the maximum possible predicted carrier value is 0.5 (i.e., for an individual with no offspring and no paternal data whose mother is a presumed carrier).

Standardized incidence ratios (SIR) and 95% Confidence Intervals were calculated for breast and ovarian cancer. In each instance, the number of affected mothers and sisters reported by controls was compared to the age- and site-specific incidences from the 1993-1997 Surveillance, Epidemiology, and End Results (SEER) centers.

RESULTS

The general makeup of the case and control subjects matched well to that of the state of Connecticut. Approximately 91% percent of cases and 92% of controls were white with the remaining sample representing primarily women of African-American background. The mean age for cases was not statistically different from that for controls (56.8 versus 55.9 years).

Unadjusted odds-ratios for a family history of breast and ovarian cancer in first and second degree relatives is presented by histologic subtype in Table 1. Both DCIS and LCIS cases were significantly more likely than controls to report at least one first degree female relative affected with breast

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cancer (OR: 1.68, 95CI: 1.31, 2.14 and OR: 1.85, 95CI: 1.17, 2.93) for DCIS

and LCIS, respectively. A higher proportion of DCIS cases than controls

reported a mother (OR: 1.30, 95CI: 0.97, 1.75) or sister (OR: 2.54, 95CI:

1.73, 3.74), but not a daughter (OR: 0.59, 95CI: 0.15, 2.36) affected with

breast cancer. LCIS cases reported a significantly increased risk for mothers

and an elevated (but not significantly so) risk for sisters. DCIS cases with

both an affected mother and sister were at 2.62 times (95CI: 0.94, 7.27) the

risk of controls without such a history. Both DCIS and LCIS cases with at

least one second degree relative affected with breast cancer were at increased

risk for DCIS (OR: 1.20, 95CI: 0.95, 1.50 and OR: 1.45, 95CI: 0.93, 2.25) for

DCIS and LCIS, respectively. Although many of the point estimates for second

degree relatives were elevated, none of the odds ratios for individual second

degree relatives differed significantly from one, with the exception of

maternal aunts among DCIS cases. There were no male relatives reported to have

breast cancer among any of the study subjects.

The risks associated with a family history of ovarian cancer are also

presented in Table 1. DCIS cases were 1.30 (95CI: 0.72, 2.34) times more

likely than controls to report a first degree relative affected with ovarian

cancer. A higher proportion of DCIS cases than controls reported a mother (OR:

1.34, 95CI: 0.67, 2.71) or sister (OR: 1.18, 95CI: 0.41, 3.38) affected with

ovarian cancer although neither estimate differed significantly from one. No

study subject reported a daughter or more than one first degree relative

affected with ovarian cancer. The estimates for women with second degree

family members affected with ovarian cancer as well as family members affected

with both breast and ovarian cancer are also presented; in general, the number

of affected relatives among these individuals is extremely small, making

interpretation of these values difficult.

Table 2 provides data on the risk of DCIS stratified by the age at onset

and the laterality of first degree relatives affected with breast cancer. In

general, as is true for IBD, increased risk was associated with early age at

onset and bilateral disease. Table 3 presents data which examines the effect

of a family history by age at onset of the DCIS cases themselves. An inverse

association between age at onset and DCIS risk is suggested with women aged 49

years or younger at 2.36 (95CI: 1.47, 3.77) times the risk of controls versus

1.47 (95CI: 1.10, 1.96) for women older than 49 years. In general, this

pattern is seen throughout the table.

To help assess the quality of family history reporting in these data,

SIRs were calculated for mothers and sisters of controls. Although the value

for both breast and ovarian cancer (0.77 and 0.87, respectively) indicate that

there is some under-reporting of both breast and ovarian cancer among first

degree relatives of controls, neither estimate differed significantly from one

and both are similar to reports from other large case/control studies which

collected family history data.[29] In addition, further analysis of the data

indicated that cases and controls were equally likely to report cancer at an

unknown site in a first degree relative, suggesting that elevations in BCIS

risk associated with a family history do not appear to be a result of less

knowledge of family history of cancer among controls as compared to cases.

In addition to examining unadjusted odds ratios, the association between

BCIS risk and family history was also calculated while controlling for

potential confounders such as age, parity, age at first full-term pregnancy,

age at first menstrual period, history of breast biopsy, use of oral

contraceptives (ever/never), use of hormone replacement therapy (ever/never),

race (white/other), and mammographic screening history one year prior to

interview. In general, the risk estimates were little changed in the adjusted

analyses.

The distribution of predicted BRCA1 and BRCA2 carrier probabilities among

DCIS cases and controls are presented by ten-year age groupings in Table 4.

The mean BRCA1 carrier probability differed significantly by both age at onset

and case/control status while the BRCA2 probability differed significantly by

case/control status. When "carriers" are defined as individuals with

calculated probabilities of 0.5 or greater, 0.1%, 0%, and 0.8% of the DCIS

cases would be predicted to carry mutations in BRCA1, BRCA2, or either of the

two, respectively. Regardless of the criteria used, no control subject was

predicted to carry a deleterious allele in either BRCA1 or BRCA2.

DISCUSSION

The present study is the largest case-control study to date to examine

the relationship of a family history of breast and ovarian cancer with BCIS

risk. The results confirm the importance of a positive family history of

breast cancer and seem to suggest, as is true for IBD, that individuals with

multiple first degree family members diagnosed with breast cancer,

particularly at young ages, are at even greater risk. A number of previous

analyses have examined the association between a history of breast cancer in

at least one first degree relative and BCIS and reported odds ratios ranging

from 1.6 to 2.7.[10-14] The current study supports this finding in a large sample

including women of all ages and with correction for screening, with odds
ratios of 1.7 and 1.8 for women diagnosed with DCIS and LCIS, respectively.
Women with multiple first degree relatives affected with breast cancer, in
particular, a mother and sister affected with breast cancer, were at even
greater risk (OR = 2.6). The one previous study able to examine risk for women
with both an affected mother and sister also reported an increased risk,[10]
however, the magnitude of that risk (OR: 6.93, 95% CI: 1.1-44) is much greater
than that seen here although the confidence interval is quite wide. It is
notable that the risk estimates for first degree relatives presented here
generally match well to studies which include women of similar age range[12] but
are somewhat lower than studies which include relatively younger women.[10,11,13]
However, when risk is dichotomized by age in these data, an inverse
relationship is seen between age at onset and risk associated with family
history with cases diagnosed by age 49 reporting a risk of 2.4, similar to
other reports which include young cases[10,11,13] versus a risk of 1.4 for cases
diagnosed over the age of 49 years. A positive association between family
history and LCIS risk was also suggested in these data as has been reported
elsewhere.[10,16]In general, the overall results for LCIS cases match those of the
DCIS cases; however, extensive sub-analyses of LCIS cases by age at onset and
laterality of relatives was not possible given the relatively small number of
LCIS cases.

Among first degree relatives, the risk associated with an affected sister
was greater than that associated with an affected mother, although not
significantly so. Other studies also indicate that risk does not differ by the
type of first degree relative affected[3,6] although the point estimates vary in

13

whether the mother or sister is associated with higher risk. As has been shown

for IBD, one possible model suggested by an equal risk to mothers and sisters

and a small proportion of genetic cases is a model incorporating a rare

autosomal dominant allele(s).

The role of ovarian cancer in the prediction of BCIS is less clear in

these data. Although increased odds ratios were observed among DCIS cases with

affected first degree relatives, none of the estimates differed significantly

from one. The data associated with second degree relatives was difficult to

interpret given the small numbers of affected relatives. This lack of

association may represent a true finding but is likely due in part to an

insufficient level of statistical power to detect a significant effect despite

the relatively large size of the sample.

Given the findings here, at least with respect to breast cancer family

history, it is of interest to attempt to assess the role that BRCA1 and BRCA2

may play in the development of BCIS. A review[10-13,16] of stage-specific risk

estimates associated with a breast cancer family history (used as a proxy

variable for BRCA1 and BRCA2 status) provides no convincing evidence that the

magnitude of risk associated with family history differs significantly by

stage with some studies reporting a greater[11,16] association with BCIS or

"early" stage lesions while others report the opposite.[12] While there are

extensive laboratory data[30-40] which estimate the prevalence of mutations in

BRCA1 and BRCA2 for women with as well as without a current diagnosis of

breast and/or ovarian cancer, there is currently little such data collected

for women diagnosed with "pure" BCIS (although researchers have noted BCIS

associated with IBD in BRCA1/BRCA2 carriers).[41] In this report, an attempt was

made to estimate the extent to which BRCA1 and BRCA2 might be involved in BCIS via the use of statistical modeling. The results obtained indicate that while there does appear to be some evidence that cancer susceptibility alleles play a role in the development of BCIS, the prevalence of such mutations may be decreased relative to that found in invasive cases.[30-40]

As is true of all statistical models of risk, accurate calculation of carrier probability depends upon a correctly specified statistical model as well as correct estimates of penetrance and prevalence. Two[28,42] groups of independent investigators have undertaken validation studies of the carrier probability model used here. Both have reported a good overall predictive ability in identifying the presence of a mutation at either gene. Efforts are under way for a systematic multicenter validation of the model based on tested families. Statistical methodology and preliminary results are discussed by Iversen et al (1998).[43] Additional caveats apply; there are initial indications that the currently used values of penetrances and prevalences may lead to underestimating carrier probabilities for weak family histories. This is consistent with the belief that the penetrance functions currently utilized may be too high for families with weak histories. Although the women in this analysis were defined as carriers and non-carriers based on a generalized statistical model, these assignments may not hold true at the individual level. Women with low to moderate risk based on family history and ethnic background may still test positive for BRCA1 and BRCA2 mutations. The final determination of carrier status and the remaining role of family history will thus be a continually changing process as the collection of laboratory data proceeds.

Few studies have examined any aspect of the genetic epidemiology of BCIS; to our knowledge, the current study is the largest done to date. The data here provide evidence that mechanisms similar to those involved in the development of IBD may be at work here, although perhaps to a lesser extent. Whether this is evidence that BRCA1 and BRCA2 are more likely to be associated with a diagnosis of IBD versus BCIS remains to be confirmed using laboratory data. One advantage of the data presented here is that the full spectrum of age at onset and histology was included as was information on screening; the estimates of risk presented here should be relatively free of screening bias, particularly important in the analysis of non-invasive tumors which are more likely to be diagnosed at an early stage using screening procedures such as mammograms.

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Table 1. Unadjusted Odds Ratios (OR) for BCIS according to family history, stratified by case histology.					
	Number of			OR (95% CI)	
	DCIS	LCIS	Controls	DCIS	LCIS
Breast Cancer Family History					
None	536	73	720	1	1
First Degree	178	28	137	1.68 (1.31, 2.14)	1.85 (1.17, 2.93)
Mother	103	21	96	1.30 (0.97, 1.75)	1.93 (1.16, 3.24)
Sister	83	7	41	2.54 (1.73, 3.74)	1.41 (0.62, 3.21)
Daughter	3	0	6	0.59 (0.15, 2.36)	N.A.
Mother and Sister	11	0	5	2.62 (0.94, 7.27)	N.A.
Second Degree	178	30	182	1.20 (0.95, 1.50)	1.45 (0.93, 2.25)
Maternal Grandmother	35	4	40	1.03 (0.65, 1.64)	0.81 (0.28, 2.29)
Paternal Grandmother	17	5	28	0.71 (0.39, 1.31)	1.47 (0.56, 3.87)
Maternal Aunt	88	9	62	1.75 (1.25, 2.45)	1.19 (0.58, 2.46)
Paternal Aunt	64	13	67	1.14 (0.80, 1.62)	1.64 (0.88, 3.07)
Ovarian Cancer Family History					
None	805	121	957	1	1
First Degree	24	2	22	1.30 (0.72, 2.34)	0.73 (0.17, 3.18)
Mother	17	1	15	1.34 (0.67, 2.71)	0.54 (0.70, 4.10)
Sister	7	1	7	1.18 (0.41, 3.38)	1.16 (0.14, 9.51)
Daughter	0	0	0	N.A.	N.A.
Mother and Sister	0	0	0	N.A.	N.A.
Second Degree	17	1	22	0.91 (0.48, 1.72)	0.36 (0.49, 2.72)
Maternal Grandmother	3	0	9	0.39 (0.11, 1.45)	N.A.
Paternal Grandmother	0	0	2	N.A.	N.A.
Maternal Aunt	8	0	4	2.37 (0.71, 7.91)	N.A.
Paternal Aunt	6	1	7	1.01 (0.34, 3.02)	1.16 (0.14, 9.51)
Breast and Ovarian Family History					
First Degree	6	0	4	1.78 (0.50, 6.31)	N.A.
Second Degree	4	0	7	0.67 (0.20, 2.30)	N.A.
Any Combination	16	1	14	1.35 (0.68, 2.79)	0.58 (0.7, 4.42)

Table 2. Unadjusted Odds Ratios (OR) for DCIS according to age and laterality of relative's breast cancer.		
	OR (95% CI)	
	Relative age <= 49	Relative age >49
Breast Cancer Family History		
First Degree	1.93 (1.25, 2.98)	1.58 (1.19, 2.10)
Mother	1.36 (0.70, 2.63)	1.29 (0.94, 1.78)
Sister	2.74 (1.51, 5.00)	2.41 (1.47, 3.94)
	Bilateral	**Unilateral**
First Degree	2.12 (1.08, 4.15)	1.62 (1.26, 2.10)
Mother	1.75 (0.74, 4.12)	1.26 (0.92, 1.71)
Sister	2.26 (0.75, 6.76)	2.58 (1.71, 3.88)

Table 3. Unadjusted Odds Ratios (OR) for DCIS according to family history, stratified by age at onset[a].		
	OR (95% CI)	
	DCIS <= 49	DCIS >49
Breast Cancer Family History		
Any	1.60 (1.14, 2.240	1.45 (1.14, 1.85)
First Degree	2.36 (1.47, 3.77)	1.47 (1.10, 1.96)
<= 49	2.54 (1.24, 5.22)	1.64 (0.95, 2.83)
> 49	2.24 (1.24, 4.04)	1.42 (1.03, 1.96)
Mother	1.68 (0.98, 2.86)	1.16 (0.82, 1.66)
Sister	4.62 (1.85, 11.5)	0.59 (0.15, 2.35)
Mother and Sister	2.38 (0.22, 26.4)	2.67 (0.82, 8.73)
Second Degree	1.13 (0.77, 1.65)	1.24 (0.93, 1.65)
Ovarian Cancer Family History		
First Degree	1.19 (0.41, 3.40)	1.34 (0.67, 2.72)
Second Degree	0.78 (0.32, 1.95)	1.06 (0.43, 2.63)
Breast and Ovarian Cancer Family History		
First Degree	2.38 (0.22, 26.4)	1.57 (0.35, 7.06)
Second Degree	1.19 (0.24, 5.93)	0.29 (0.03, 2.63)
Any Combination	2.10 (0.61, 7.25)	1.06 (0.43, 2.63)

a. Cases are matched to controls by control age at interview

Table 4. Age-specific estimates of BRCA1 and BRCA2 carrier probability						
BRCA1						
	DCIS cases			**Controls**		
	Mean (S.D.)	Minimum	Maximum	Mean (S.D.)	Minimum	Maximum
Age Group						
<=39	0.0512 (0.0958)	0.0011	0.452	0.0012 (0.0039)	0.000032	0.0307
40-49	0.0233 (0.0534)	0.0005	0.345	0.0008 (0.0046)	0.000013	0.0585
50-59	0.0145 (0.0529)	0.0002	0.618	0.0003 (0.0009)	3E-6	0.0082
60-69	0.0109 (0.0552)	2E-5	0.195	0.0004 (0.0029)	3E-6	0.0390
70-79	0.0017 (0.0124)	4E-5	0.139	0.0002 (0.0005)	3E-6	0.0037
BRCA2						
	Mean (S.D.)	Minimum	Maximum	Mean (S.D.)	Minimum	Maximum
Age Group						
<=39	0.0105 (0.0252)	0.0007	0.153	0.0006 (0.0020)	0.000019	0.0155
40-49	0.0110 (0.0336)	0.0002	0.265	0.0008 (0.0068)	9E-6	0.1144
50-59	0.0132 (0.0483)	0.0001	0.475	0.0004 (0.0015)	2E-6	0.0158
60-69	0.0109 (0.0552)	4E-5	0.491	0.0004 (0.0029)	2E-6	0.0427
70-79	0.0058 (0.0396)	1E-6	0.394	0.0002 (0.0005)	1E-6	0.0057

DEPARTMENT OF THE ARMY
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REPLY TO
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                              PHYLIS M. RINEHART
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